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Proximal Trisomy 1q in a Girl With Developmental Delay and Minor Anomalies

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We report on a girl with developmental delay, macrocephaly, facial asymmetry, small downturned palpebral fissures, high and narrow palate, micrognathia, short neck, a heart defect, and unilateral renal agenesis. Cytogenetic analysis showed a proximal tandem duplication of the long arm of chromosome one (1q12→q21.3). This abnormality was suggested by G- and C-banding but it was specifically characterized by fluorescent in situ hybridization (FISH). Clinical findings in our patient are compared with those of the literature in an attempt to delineate the phenotype in patients with proximal 1q duplication. © 1996 Wiley-Liss, Inc.

KEYWORDS: proximal 1q tandem duplication, dup(1q), partial trisomy 1q, fluorescent in situ hybridization (FISH)

INTRODUCTION

Tandem duplications are useful to study the phenotype associated with specific chromosome imbalances because they are not concurrent with deletions of other chromosome segments [van Dyke, 1988]. Proximal tandem duplications of 1q are rare; to our knowledge two cases have been reported previously [Mertens et al., 1987; Chen et al., 1994]. Furthermore, a case of a der(Y)t(Y;1) mosaic [Watson et al., 1990], including the proximal part and extending to the terminus of 1q, has also been reported.

Fluorescent in situ hybridization (FISH) with whole chromosome paints is an important tool for marker chromosome identification when standard banding techniques have been uninformative [Kraker et al., 1992] and a valuable help providing a rapid, unequivocal cytogenetic diagnosis for patients with de novo chromosomal duplications [Leana-Cox et al., 1993].

We present a new case of proximal tandem duplication of the long arm of chromosome 1, unequivocally identified by FISH. Clinical findings in the previously reported cases are compared with those of our patient.

CLINICAL REPORT

The proposita is the only child of non-consanguineous parents. At birth, both parents were 22 years old and the family history was unremarkable. The mother had been exposed to ammonium and paint smells during pregnancy. The child was born at term, through vaginal delivery. Birth weight was 2,950 g, birth length was not available, though she was referred to as rather short. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. A neonatal tooth and a slightly anteriorly placed anus were noted.

She was referred at 11 months because of macrocephaly with a wide anterior fontanelle and failure to thrive. At that time her length was 68.5 cm (3rd centile) and her OFC was 44.8 cm (25th centile).

The patient had facial asymmetry, a forehead with lateral prominences, brittle and sparse hair, short downturned palpebral fissures, deep-set and widely spaced eyes, a flat and broad nose with a short columella, an open mouth with downturned corners, a thin upper and an everted lower lip, a high, narrow palate, micrognathia, and a short neck. The ears were big and posteriorly angulated (Fig. 1a,b). The chest was shield-shaped, with low and widely spaced nipples and the lower limbs showed genua valga (Fig. 2). The hands were small with short, tapered and slightly webbed fingers, clinodactyly of the fifth fingers, and prominent distal finger pads (Fig. 3). External genitalia were hypoplastic and an abdominal ultrasound scan showed unilateral renal agenesis. She had had recurrent otitis and constipation during her first year of life, and was developmentally delayed, not being able to sit alone.

Brain ultrasound scan documented lateral ventricular enlargement and the auditory brain stem response was slightly slow. Progressive hydrocephalus was diagnosed at age 2 years. Walking started at 36 months and her dentition was delayed. A CT brain scan showed an extra-axial cyst of the posterior fossa. She had also de-

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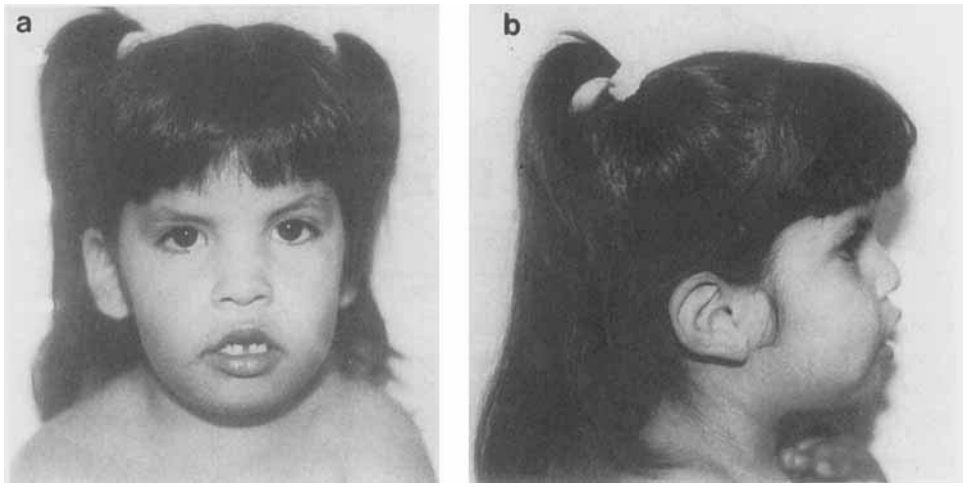

Fig. 1. Facial appearance of the patient at 3 years and 10 months of age. **a:** Frontal and (**b**) lateral view.

veloped progressive respiratory disease and recently a pulmonary artery stenosis was suspected. At 3 years and 10 months she still showed the same clinical phenotype and had developed no speech.

MATERIALS AND METHODS

Cytogenetic analysis was performed on peripheral blood lymphocytes. Cultures were established according to the method of Moorhead et al. [1960] and treated with acridine orange to produce elongated chromosomes [Matsubara et al., 1983]. The chromosomes were analyzed following GTG and CBG banding, as described by Seabright [1971] and Sumner [1972], respectively. FISH was carried out using a whole chromosome painting probe for chromosome 1 (WCP chromosome 1, Imagenetics), that was purchased from GIBCO/BRL. FISH was performed according to the standard protocol used by GIBCO/BRL.

RESULTS

The analysis of G-banded chromosomes from the patient at the 550–850 band level showed a direct duplication of the proximal part of the long arm of chromosome 1q12→q21.3 resulting in partial trisomy 1q

Fig. 2. Full body view of the patient at age 3 years and 10 months.

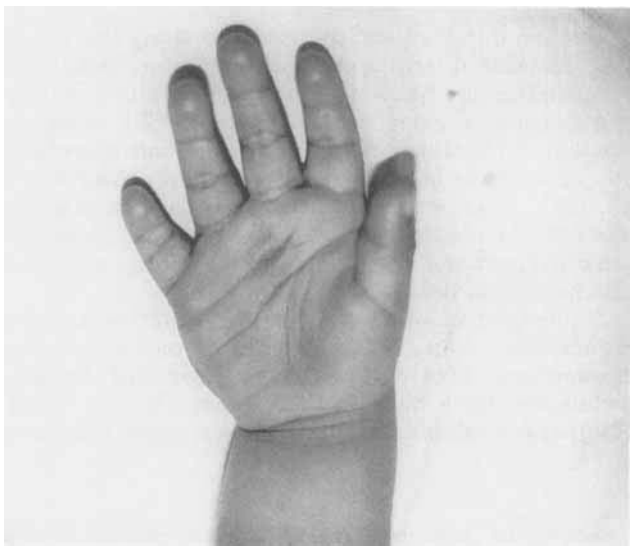

Fig. 3. Hand of the patient showing short, tapered fingers, fifth finger clinodactyly and distal finger pads.

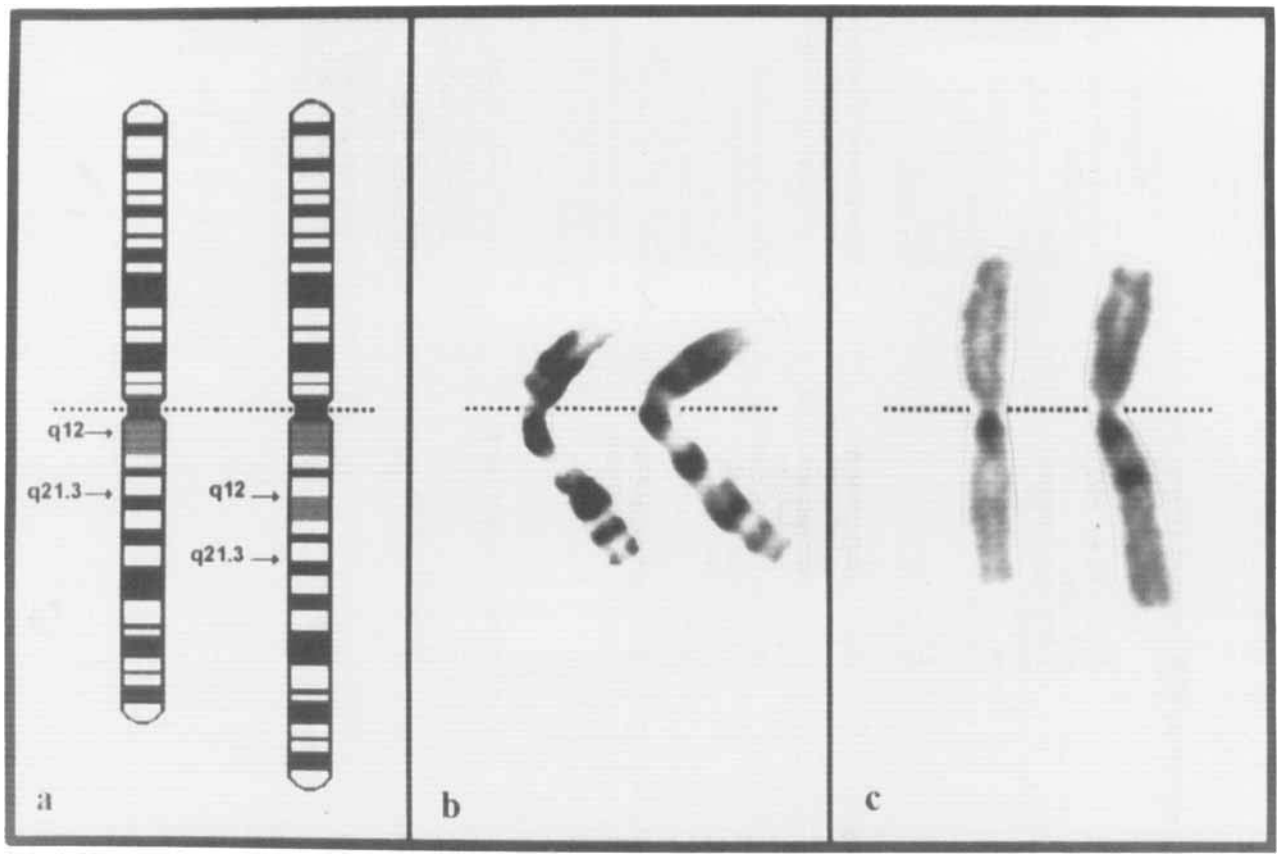

Fig. 4. **a:** Idiogram, (**b**) partial G-banded, and (**c**) C-banded karyotypes illustrating the normal (left) and the duplicated (right) chromosome 1.

(Fig. 4a,b). C-banding documented duplication of the subcentro-meric heterochromatic region (Fig. 4c). Thus, the karyotype was46,XX,dir dup(1)(pter→q21.3:: q12→qter). The chromosomes of the mother were normal; the father was unavailable for analysis.

FISH using the chromosome 1 Spectrum Green painting probe showed that the probe hybridized to both the normal and the duplicated chromosome. The normal chromosome showed a pale fluorescent area at the heterochromatic region and the duplicated one showed two pale areas corresponding to the duplicated heterochromatic region.

DISCUSSION

Manifestations common in trisomy 1q were defined through an extensive review by Du Pont et al. [1994]; however, in all of them the duplicated segment included the distal half of 1q and did not include the proximal part of 1q. Our study uncovered clinical similarities and differences between the three cases reported previously with proximal 1q duplication and our patient (Table I).

All four cases had brain anomalies, as the only consistent major defect. Interestingly, three of the cases showed anomalies of the posterior fossa and/or cerebellum, the fourth involved hydrocephalus and small temporal lobes. Other malformations were omphalocele and an omphalomesenteric duct [Mertens et al., 1986], microtia and microphthalmia [Watson et al., 1990], eventration of the left hemidiaphragm [Chen et al., 1994], heart defects [Chen et al., and present case], and unilateral renal agenesis (present case). Two of the patients had a cleft soft palate [Mertens et al., 1986; Chen et al., 1994], while the other two had a narrow palate [Watson et al., 1990 and present case]. Frequent minor anomalies were micrognathia (in all four cases), ear anomalies, prominent and/or upturned nose, long philtrum, and joint anomalies (three of four cases). The mortality in one of the cases could also be due to the twinning [Watson et al., 1990], and in the other to the diaphragmatic hernia [Chen et al., 1994], which suggests that a duplication of the proximal part of chromosome 1 is not associated with high perinatal mortality in absence of severe malformations.

In spite of some clinical similarities, we were not able to detect a clear correspondence between the cytogenetic and the clinical findings, nor do we think that any of the described manifestations would allow the diagnosis of a proximal duplication of 1q to be suspected. This could depend first on the extension of the non-overlapping duplicated segment of chromosome 1, and second on the small number of described cases which does not allow an outlining of the clinical phenotype which largely depends on minor features. Conse-

TABLE I. Clinical and Cytogenetics Findings in Patients With Proximal Trisomy 1q*

	Mertens et al. [1987]	Chen et al. [1994]	Watson et al. [1990]	Present case
Karyotype	invdup(1)(q11→q22)	dir dup(1)(q12→q25)	der(Y)t(Y;1)(q12;q21)	dirdup(1)(q12→q21.3)
Duplication	q11→q22	q12→q25	q21→qter	q12→q21.3
Deletion	None	None	Y q12→qter (mosaic)	None
Gestation	37 wk	Term	30 wk	Term
Sex	M	M	M	F
Birth weight	2,880 g	3,260 g	1,570 g	2,950 g
Birth length	48 cm	37 cm	–	Short
APGAR	3-6-9	1-5	2-1	9-10
Age last seen or at demise	11 mo	2 wk (D)	30 min (D)	3 yr 10 mo
Brain/head	Slight asymmetry of posterior fossa and cerebellum	Mild microbrachycephaly, mild hydrocephaly, small temporal lobes	Macrocephaly, severe hydrocephalus, ventricular enlargement, hypoplastic cerebellum	Enlargement of lateral ventricles, hydrocephaly, cyst of posterior fossa
Eyes	Narrow palpebral fissures	–	Microphthalmia, complete coloboma, retinal dysplasia	Mild hypertelorism, narrow palpebral fissures
Ears	Low-set, malformed[a]	Low-set, malformed[a]	Microtia	Posteriorly rotated
Nose	Prominent upturned[a]	Prominent[a]	Prominent[a]	Broad and flat bridge
Chin/mouth	Micrognathia, cleft palate, long philtrum[a]	Micrognathia,[a] cleft palate, long philtrum[a]	Micrognathia, narrow palate, microstomia	Mild micrognathia, high narrow palate, long philtrum
Skin/hair	Excessive skin in neck	Wrinkled skin	–	Sparse dry hair
Joints	Flexion contractures, feet dorsal flexion	Flexion contractures, equinovarus	–	N
Hands	–[b]	Overlapping fingers	Bilateral camptodactyly	Small hands, distal finger pads, fifth fingers clinodactyly
Thorax	–	–	Shield-like chest	Shield-like chest
Genitourinary	N	Right cryptorchidism	N	Unilateral renal agenesis, hypoplastic external genitalia
Others	Omphalocele, omphalomesenteric duct	Ductus arteriosus and foramen ovale, pulmonary hypoplasia, eventration of left hemidiaphragm	Twinning	Neonatal tooth, pulmonary artery stenosis suspected
Psychomotor development	Severely retarded	–	–	Retarded, no language

* N, normal; M, male; min, minutes; wk, weeks; mo, months; yr, years; D, deceased.
[a] Judged from published photography.
[b] –, Not mentioned in report.

quently, the report of other patients with this chromosome abnormality is encouraged.

On the other hand, the co-existence of an anomalous posterior fossa, a heart defect, and some minor anomalies of face and hands in our patient shows certain similarities with a sibship reported by Ritscher et al. [1987], though in these patients the heart anomaly was an atrioventricular septal defect, no chromosomal anomaly was detected, and the condition was thought to be autosomal recessive. Furthermore, the pattern of minor anomalies plus a suspected pulmonary artery stenosis in our patient could suggest a Noonan-like phenotype. To our knowledge, until now there has been no report in the literature associating Noonan syndrome with anomalies of chromosome 1.

The definite identification of the proximal duplication of chromosome 1q by FISH emphasizes the usefulness of chromosome painting probes for a more accurate diagnosis in medical genetics.

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REFERENCES

Chen H, Kusyk CJ, Tuck-Muller CM, Martinez JE, D'Dorand R, Wertelecki W (1994): Confirmation of proximal 1q duplication using fluorescence in situ hybridization. Am J Med Genet 50:28–31.

Du Pont BR, Huff RW, Ridgway LE, Stratton RF, Moore CM (1994): Prenatal diagnosis of partial trisomy 1q using fluorescent in situ hybridization. Am J Med Genet 50:21–27.

Kraker WJ, Borell TJ, Schad ChR, Pennington MJ, Kames PS, Dewald GW, Jenkins RB (1992): Fluorescent in situ hybridization: Use of whole chromosome paint probes to identify unbalanced chromosome translocations. Mayo Clin Proc 67:658–662.

Leana-Cox J, Levin S, Surana R, Wulfsberg E, Keene CL, Raffel LJ, Sullivan B, Schwartz S (1993): Characterization of the novo duplications in eight patients by using fluorescence in situ hybridization with chromosome-specific DNA libraries. Am J Hum Genet 52: 1067–1073.

Matsubara T, Nakagome Y (1983): High resolution banding by treating cells with acridine orange before fixation. Cytogenet Cell Genet 35:148–151.

Mertens F, Johansson B, Forslund M, Olsson M, Kristoffersson U (1987): Tandem duplication (1)(q11→q22) in a male infant with multiple congenital malformations. Clin Genet 32:46–48.

Moorhead PS, Nowell PC, Mellman WJ, Battips DM, Hungerford DA (1960): Chromosome preparations of leukocytes cultured from human peripheral blood. Exp Cell Res 20:613–616.

Ritscher D, Schinzel A, Boltshauser E, Briner J, Arbenz U, Sigg P (1987): Dandy Walker (like) malformation, atrio-ventricular septal defect and a similar pattern of minor anomalies in 2 sisters: A new syndrome? Am J Med Genet 26:481–491.

Seabright M (1971): A rapid banding technique for human chromosomes. Lancet 2:971–972.

Sumner AT (1972): A simple technique for demonstrating centromeric heterochromatin. Exp Cell Res 75:304–306.

van Dyke DL (1988): Isochromosomes and interstitial tandem direct and inverted duplications. In Daniel A (ed): The Cytogenetics of Mammalian Autosomal Rearrangements. New York: Alan R. Liss, Inc., pp 635–665.

Watson WJ, Katz VL, Albright SG, Rao KW, Aylsworth AS (1990): Monozygotic twins discordant for partial trisomy 1. Obstet Gynecol 76:949–951.